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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/699,030	10/26/2000	Shiy Kumar	030516.0029CON1	3324

7590 01/21/2003
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EXAMINER

FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
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1637

DATE MAILED: 01/21/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/699,030

Applicant(s)

KUMAR ET AL.

Examiner

Jeffrey Fredman

Art Unit

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 December 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17 is/are pending in the application.
- 4a) Of the above claim(s) 14-17 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 5-8 and 10-13 is/are allowed.
- 6) ☒ Claim(s) 1-4 and 9 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☒ Interview Summary (PTO-413) Paper No(s) 9.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Priority

1. Applicant's amendment to refer to the related application in the first sentence places the application in compliance with the conditions for receiving priority to 09/018,695 and priority is granted.

Sequence Rules

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because there is no CRF and because the sequence in figure 1 is not in the paper copy of the Sequence Listing.
3. Applicant requests a transfer of the sequence from the parent application and requests a telephone call if the sequence of figure 1 is required to be included in the sequence listing. See attached interview summary regarding the telephone call. With regard to the inclusion of the sequence of figure 1, MPEP 2421.02 makes it clear that "The rules apply to all sequences in a given application, whether claimed or not. All such sequences are relevant for the purposes of building a comprehensive database and properly assessing prior art. It is therefore essential that all sequences, whether only disclosed or also claimed, be included in the database." The sequence in figure 1 is disclosed and must therefore be included in the Sequence listing.

4. A complete response to this action will require compliance with the Sequence Rules. No afterfinal amendment in which the application fails to comply with sequence rules will be entered or considered.

Claim Rejections - 35 USC § 112

5. The rejection under 35 U.S.C. 112, second paragraph is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 102

6. Since Applicant has complied with the priority requirements, as noted above and required in the previous action, the Kumar reference is no longer prior art and the rejection under 35 U.S.C. 102 is withdrawn.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 3 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evangelista et al (Anal. Biochem. (1996) 235:89-97).

Evangelista teaches a compound of formula (I) (A-B-C) with a cyanine dye which meets the structural requirements of A, a linker of more than 10 atoms in length as required by B, and attached to the 5 position of dUTP, which has a triphosphate attached (page 91, figure 1). It should be noted, that because the attachment is at the 5 position, dUTP and dTTP yield identical structures.

Evangelista does not teach a structure where this compound is a dideoxynucleotide.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to modify the labeled deoxynucleotide of Evangelista into a dideoxynucleotide since Evangelista notes "Fluor-labeled deoxynucleotide triphosphates (dNTPs) or dideoxynucleoside triphosphates (ddNTPs) are employed in nonradioactive DNA sequencing techniques such as those developed by Prober et al (ref omitted) and Ansorge et al (ref omitted) as well as for incorporation into hybridization probes (ref omitted). Fluorescent ddNTPs have also been used as terminal deoxynucleotidyl transferase substrates to label single (ref omitted) and double stranded DNA (ref omitted) (page 89, column 1, last sentence to page 89, column 2)". An ordinary practitioner would have been motivated to alter the dNTP dyes of Evangelista into ddNTP dyes in order to permit nonradioactive DNA sequencing,

hybridization probe or terminal transferase methods to be used as expressly taught by Evangelista. An ordinary practitioner would have had a very high expectation of success since it is routine to make both dNTP and ddNTPs with the same label as discussed by Evangelista on page 89, column 2. It would have been further obvious to utilize the ddNTP resulting from this synthesis in a DNA sequencing method to yield a DNA which comprises the ddNTP.

10. Claims 1-3 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evangelista et al in view of Tabor et al (U.S. Patent 5,614,365).

Evangelista teaches a compound of formula (I) (A-B-C) with a cyanine dye which meets the structural requirements of A, a linker of more than 10 atoms in length as required by B, and attached to the 5 position of dUTP, which has a triphosphate attached (page 91, figure 1). It should be noted, that because the attachment is at the 5 position, dUTP and dTTP yield identical structures. Evangelista further notes "Our DNA labeling results indicate that the distance provided by the 10-atom spacer arm between the pyrimidine ring and the rather bulky cyanine label is sufficient to allow base pairing between the deoxyadenosine and deoxyuridine at the ends of the DNA fragments (page 97, column 1)".

Evangelista does not teach the use of a modified thermostable polymerase nor does Evangelista teach placement of the reagents into a kit.

Tabor teaches the use of modified thermostable polymerases in DNA sequencing reactions (column 5, lines 38-58). Tabor further teaches placement of the reagents into a kit (column 9, lines 57-62).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the fluorescently labeled ddNTPS which are made obvious by Evangelista into a kit with the modified thermostable polymerases of Tabor since Tabor notes "By modification of these enzymes using methods shown below, those in the art can now modify any desired thermophilic DNA polymerase to make it incorporate dideoxynucleotides more efficiently. Such enzymes will be superior to those existing in the present day for DNA sequencing both in automated machines and in manual sequencing, especially in procedures known as cycle sequencing (column 5, lines 46-53)". An ordinary practitioner would have been motivated to form a kit with ddNTPs as made obvious by Evangelista for the improved sensitivity of the dyes (page 96, column 2) as shown by Evangelista and for the use of a superior enzyme as expressly taught by Tabor. An ordinary practitioner would have been motivated to form a kit since with the use of a kit, one need not purchase gram quantities of multiple reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. Further, the kit format saves money and resources by dramatically reducing waste. The other advantage provided in a kit is quality control.

11. Claims 3, 4 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evangelista in view of Haralambidis et al (Nucleic Acids Research (1987) 15(12):4857-4876).

Evangelista teaches a compound of formula (I) (A-B-C) with a cyanine dye which meets the structural requirements of A, a linker of more than 10 atoms in length as required by B, and attached to the 5 position of dUTP, which has a triphosphate

attached (page 91, figure 1). It should be noted, that because the attachment is at the 5 position, dUTP and dTTP yield identical structures. Evangelista further notes "Our DNA labeling results indicate that the distance provided by the 10-atom spacer arm between the pyrimidine ring and the rather bulky cyanine label is sufficient to allow base pairing between the deoxyadenosine and deoxyuridine at the ends of the DNA fragments (page 97, column 1)".

Evangelista does not teach the specific linkers of claim 4.

Haralambidis teaches a linker (page 4860, figure 1) which is identical to the fourth claimed linker of claim 4, where the linker links to a nitrogen, as occurs in the structure of Evangelista.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the dye labeled compound rendered obvious by Evangelista with the linker of Haralambidis since Haralambidis states "In this paper we have described a method for the synthesis of C-5 substituted deoxyuridine nucleosides, with the substituent carrying a masked primary aliphatic amino group. This method is exceptionally mild and gives the desired compound in high yield (page 4874)". Haralambidis further notes "It was found that oligonucleotides carrying a long (11 atom) linker arm to the fluorescein hybridize more efficiently to mRNA than those carrying a short (4 atom) arm (abstract, page 4857)". An ordinary practitioner would have been motivated to utilize the long linker arm of Haralambidis in the synthesis of the cyanine dye of Evangelista for the expressly stated benefits of mild conditions, high yield and efficient hybridization.

Allowable Subject Matter

12. Claims 5-8 and 10-13 are allowed.
13. The following is a statement of reasons for the indication of allowable subject matter: These claims are drawn to compounds with specific structural formula which are not taught or suggested by the cited prior art such as Evangelista.

Response to Arguments

14. Applicant's arguments filed December 18, 2002 have been fully considered but they are not persuasive.

Applicant first argues that ddNTPs would not be used in the applications described in Evangelista. This argument is incorrect since Evangelista clearly envisions the use of the labeled nucleotides in automated sequencing type assays (see page 94, column 1). Such assays routinely use labeled ddNTPs for labeling. So when Evangelista teaches the label and suggests the use of the label in sequencing type reactions, this is a direct suggestion to make labeled ddNTPs.

Applicant then argues that there may be some hypothetical problem in the use of ddNTPs. This argument is not found persuasive for several reasons. First, MPEP 716.01(c) makes clear that

"The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant."

Here, the statements regarding any potential difficulties must be demonstrated, not simply argued. Second, Applicant may be arguing that this is an "obvious to try" situation. The legal standard for "reasonable expectation of success" is provided by caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not require absolute predictability, only a reasonable expectation of success; i.e., a reasonable expectation of obtaining similar properties. See, e.g., *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)." In this factual case, there is express suggestion in the prior art that the labels of Evangelista would function and be incorporated by polymerases. There is further evidence as shown in figures 4 and 5 of Evangelista that the labeled dNTPs were, in fact, incorporated by polymerases. This is sufficient for a reasonable expectation of success in incorporation of ddNTPs. The MPEP cites *In re O'Farrell*, which notes regarding "obvious to try" at page 1682, that,

"In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. E.g., *In re Geiger*, 815 F.2d at 688, 2 USPQ2d at 1278; *Novo Industri A/S v. Travenol Laboratories, Inc.*, 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); *In re Yates*, 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); *In re Antonie*, 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. *In re Dow Chemical Co.*, 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed.

Art Unit: 1637

Cir. 1985); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1986), cert. denied, 107 S.Ct. 1606 (1987); *In re Tomlinson*; 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966).

The court in *O'Farrell* then, affirming the rejection, notes " Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. This is not a situation where the prior art suggests varying a variety of parameters, since the prior art directly points to the use of ddNTPs in suggesting the use of the labeled nucleotides in automated sequencing methods. This is also not a situation where only general guidance was given. The prior art provides specific guidance directing the use of nucleotides in polymerase assays.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, specific motivation is provided in the rejections.

Conclusion


15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Jeffrey Fredman
Primary Examiner
Art Unit 1637

January 17, 2003